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RESEARCH ARTICLE

Pathogenesis of obstructive sleep apnea in people living with HIV

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Abstract

Obstructive sleep apnea (OSA) is highly prevalent in people living with human immunodeficiency virus (HIV) (PLWH), and it might contribute to frequently reported symptoms and comorbidities. Traditional risk factors for OSA are often absent in PLWH, suggesting that HIV or HIV medications might predispose to OSA. Therefore, we measured the anatomical and nonanatomical traits important for OSA pathogenesis in those with and without HIV. We recruited virally suppressed PLWH who had been previously diagnosed with OSA (PLWH + OSA) adherent to positive airway pressure (PAP) therapy, along with age-, sex-, and body mass index (BMI)-matched OSA controls. All participants underwent a baseline polysomnogram to assess OSA severity and a second overnight research sleep study during which the airway pressure was adjusted slowly or rapidly to measure the OSA traits. Seventeen PLWH + OSA and 17 OSA control participants were studied [median age = 58 (IQR = 54–65) yr, BMI = 30.7 (28.4–31.8) kg/m^2, apnea-hypopnea index = 46 (24–74)/h]. The groups were similar, although PLWH + OSA demonstrated greater sleepiness (despite PAP) and worse sleep efficiency on baseline polysomnography. On physiological testing during sleep, there were no statistically significant differences in OSA traits (including V_{eupnea}, $V_{arousal}$, $V_{passive}$, V_{active}, and loop gain) between PLWH + OSA and OSA controls, using mixed-effects modeling to account for age, sex, and BMI and incorporating each repeated measurement (range = 72–334 measures/trait). Our data suggest that well-treated HIV does not substantially impact the pathogenesis of OSA. Given similar underlying physiology, existing available therapeutic approaches are likely to be adequate to manage OSA in PLWH, which might improve symptoms and comorbidities.

NEW & NOTEWORTHY Clinical data suggest an increased risk of obstructive sleep apnea (OSA) in people living with HIV (PLWH), while OSA might account for chronic health issues in this population. We characterized the anatomical and nonanatomical OSA traits in PLWH + OSA compared with OSA controls, using detailed physiological measurements obtained during sleep. Our data suggest against a major impact of HIV on OSA pathogenesis. Available OSA management strategies should be effective to address this potentially important comorbidity in PLWH.

fatigue; HIV; obstructive sleep apnea

INTRODUCTION

The availability of effective and well-tolerated antiretroviral therapy (ART) has led to dramatically improved survival for people living with human immunodeficiency virus (HIV) (PLWH) (1). As a result, more than 50% of PLWH in the United States are over 50 yr old (2). Although further research and efforts with regard to HIV prevention and cure are ongoing, an important current focus in clinical care is improved understanding and management of comorbidities in older PLWH. Difficulties with sleep and fatigue are common in PLWH even in those with suppressed viremia and normal CD4 counts (3–5).

Obstructive sleep apnea (OSA) is defined by repetitive collapse of the upper airway during sleep leading to transient hypoxemia and arousals from sleep. Surges in sympathetic activity, repeated oxygen desaturations, and sleep fragmentation lead to cardiovascular (e.g., hypertension, stroke, myocardial infarction), metabolic (e.g., diabetes), and neurocognitive (e.g., excessive daytime sleepiness, motor vehicle accidents) consequences (6). Recent estimates suggest that roughly 10% of the US population has clinically important OSA (roughly 13% of middle-aged men and 6% of US women), the high prevalence reflecting aging of the population and the obesity pandemic, both factors known to contribute to OSA risk

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(7, 8). In older populations, the prevalence may be much higher (9).

OSA appears to be common among PLWH, raising the question as to whether PLWH are particularly predisposed to OSA (10). One of the few studies to examine the prevalence of OSA in PLWH to date found that 70% of PLWH in their cohort had OSA (11). Although the prevalence was equally high in the HIV-negative control group, PLWH with OSA were younger and leaner compared with those without HIV. For example, only 12% of the subjects with HIV and OSA were obese in this cohort compared with 33% of HIV-negative individuals. In addition, current or prior ART use was associated with an increased prevalence of OSA compared with no prior ART exposure. These data suggest that HIV and/or ART might predispose in some way to OSA. Early reports of OSA in PLWH suggested that adenotonsillar hypertrophy with untreated HIV or ART-induced lipodystrophy and/or weight gain might predispose to OSA (12–15). The extent to which such factors are important with modern ART is an area of active investigation. In addition, we have previously demonstrated that OSA is due to anatomical as well as nonanatomical risk factors: upper airway muscle responsiveness, ventilatory control sensitivity, and respiratory arousal threshold (16). These traits can be quantified during sleep while on positive airway pressure, the level of which can be reduced slowly or suddenly to measure subject responses (17).

Thus, we sought to test the hypothesis that coexisting HIV infection leads to alterations in the anatomical or nonanatomical factors that contribute to OSA. To test this hypothesis, we measured the pathophysiological traits in age-, sex-, and body mass index-matched participants with OSA, with and without HIV.

METHODS

The research was approved by the Human Research Protections Program at the University of California San Diego (Institutional Review Board No. 161299) and was registered on clinicaltrials.gov (NCT03064204). All participants provided written informed consent.

Study Participants

Men and women were recruited via advertisements in the University Sleep and HIV Medicine Clinics, from a pool of prior research subjects, and from the community via advertisements and presentations at community-based organizations. Inclusion criteria were ages 18–70 yr, with documented HIV diagnosis on combination ART and with consistent virological suppression, and with a body mass index (BMI) of 20–35 kg/m^2. We also required participants to have diagnosed OSA (apnea-hypopnea index $\geq$5 events/h) treated with positive airway pressure (PAP) therapy (as PAP therapy can influence the measured traits) (18). Exclusion criteria were any uncontrolled cardiovascular, pulmonary, or renal disease (such as heart failure, renal disease, cirrhosis) or medications known to affect the traits important for OSA, such as narcotics or sedative-hypnotics. Appropriate HIV-positive participants with OSA (PLWH + OSA) were 1:1 case-matched with HIV-negative persons (OSA controls) on the basis of sex, age of ±5 yr, and BMI of ±3 kg/m^2 (19).

Procedures

After consent, demographic and medical history data were collected. Participants also completed questionnaires, including the Epworth Sleepiness Scale, 36-item short-form survey (SF-36), and Pittsburgh Sleep Quality Index (PSQI), and indicated confirmed recent continuous positive airway pressure (CPAP) adherence (PAP downloads were available for a minority of subjects).

A baseline polysomnography (PSG) off of PAP therapy for one night confirmed the diagnosis of OSA and assessed severity. Participants were then instrumented in the usual fashion with electroencephalogram, electrooculogram, and chin electromyogram for sleep staging; nasal pressure transducer and thermistor for air flow; respiratory impedance belts at the thorax and abdomen for respiratory effort; EKG for heart rate; and pulse oximetry. Instruction was provided to the participants to sleep in the supine position. All signals were sampled at 25–250 Hz and were acquired using a 1401 digital-analog converter and Spike2 acquisition software (Cambridge Electronic Design Ltd, Cambridge, UK).

OSA Trait Measurement

During a second night within 4 wk of the baseline PSG, participants returned to the sleep research laboratory and were instrumented in a similar fashion, except that a nasal mask and a pneumotachograph (Validyne, Northridge, CA) were placed over the nose rather than the nasal pressure transducer and thermistor. The mask was connected via a hose to a specially manufactured PAP machine (ResMed, San Diego, CA) capable of producing rapid pressure changes in the range of -20 to $+20$ cmH_2O. At sleep onset, the PAP level was adjusted to eliminate any upper airway obstruction and flow limitation. During stable nonrapid eye movement (NREM) sleep, the PAP level was decreased either rapidly or slowly as has been described previously to measure the following values and determine the traits (Fig. 1). These maneuvers were repeated multiple times throughout the night to allow for repeated measures of each variable (17).

- V_{eupnea}: The minute ventilation at the "holding pressure," that is, PAP level with no upper airway obstruction.
- $V_{passive}$: The ventilation at atmospheric pressure, determined using a series of five breath drops from holding pressure, incorporated via linear regression. $V_{passive}$ is considered the main measure of anatomy. We also measured the critical closing pressure from the initial PAP level (20).
- $V_{arousal}$: The ventilation at which arousals occur when the PAP level is decreased slowly over time. $V_{arousal}$ is a measure of propensity to develop a respiratory arousal.
- V_{active}: At the $V_{arousal}$, the ventilation when the PAP level is rapidly changed to atmospheric pressure. V_{active} is a measure of upper airway muscle responsiveness.
- Loop gain (LG): LG is the ventilatory response divided by the disturbance. During stable flow limited breathing (a disturbance from V_{eupnea}), the PAP level is increased rapidly and ventilation measured (the response).

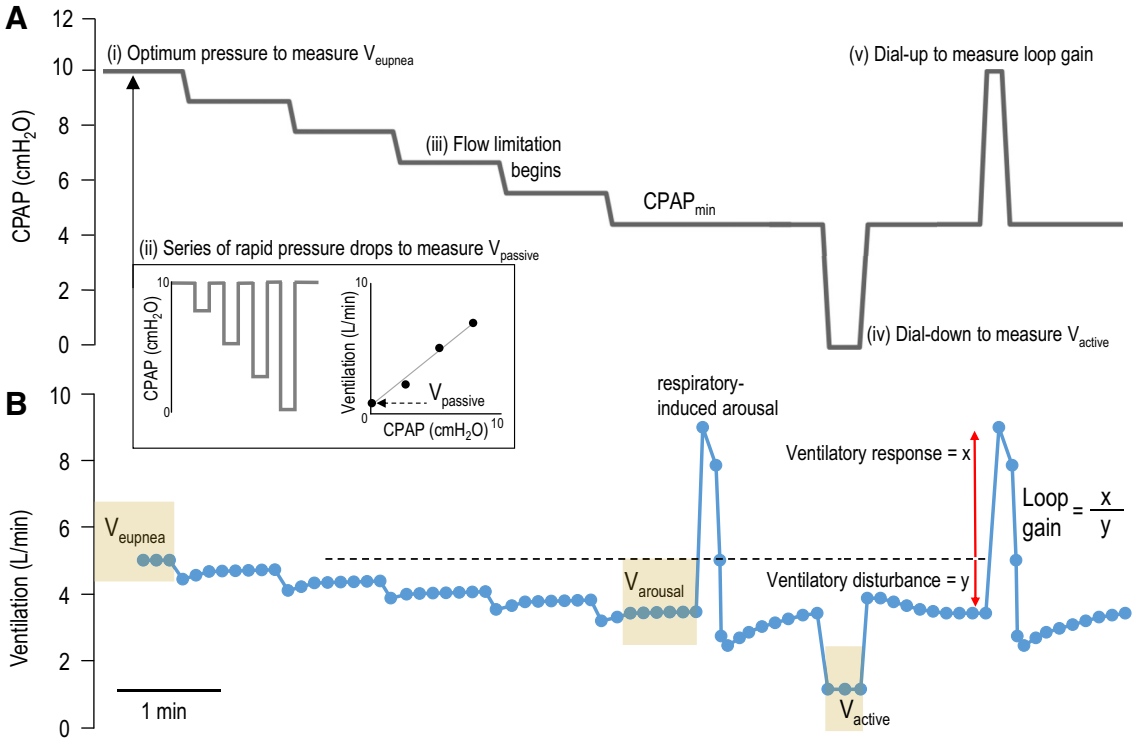

Figure 1. Measurement of OSA traits via airway pressure manipulation. OSA traits are measured by manipulating CPAP (*A*) during supine nonrapid eye movement (NREM) sleep and measuring the resultant changes in ventilation (*B*). *i*: minute ventilation is taken over 30–60 s while on optimal CPAP settings (i.e., holding pressure) to measure V_{eupnea}; *ii*: the pressure is rapidly dropped to sequentially lower pressures. Minute ventilation (for $V_{passive}$) and peak inspiratory flow (for P_{crit}) are taken from the 3rd through 5th breaths following a drop. Regression is used to determine ventilation at atmospheric pressure for $V_{passive}$ and CPAP level at onset of zero peak inspiratory flow for P_{crit}. *iii*: CPAP is then gradually lowered until flow limitation starts and arousals occur intermittently. Ventilation just before arousal is defined as $V_{arousal}$. During stable breathing between arousals under this maximally increased respiratory drive, CPAP is dialed down or up from this level to obtain V_{active} (*iv*) and loop gain (*v*), respectively. For V_{active}, minute ventilation was estimated from the 2nd and 3rd breaths following a rapid drop from the minimum tolerable CPAP level, using regression to determine ventilation at atmospheric pressure for V_{active}. Loop gain is the ventilatory response (first breath overshoot in ventilation above V_{eupnea}) divided by the ventilatory disturbance (preceding 5-breath reduction in ventilation below V_{eupnea}). CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea.

- Respiratory arousal threshold (ArTh): The ArTh is a calculated value, using the LG and V_{eupnea} data to estimate the ventilatory drive that is present at the ventilation measured by $V_{arousal}$.
- Upper airway gain (UAG): The UAG is a calculated value, using $V_{passive}$, V_{active}, V_{eupnea}, and LG to determine the increase (or decrease) in ventilation achieved with an increase in respiratory drive.

Signal Analysis

The PSGs were scored according to American Academy of Sleep Medicine criteria, with hypopneas defined by a reduction in airflow of at least 10 s leading to a 3% drop in oxygen saturation or arousal by a registered PSG technologist (RPSGT).

The physiological data were exported to MATLAB R2018a (The MathWorks, Natick, MA) and then analyzed using custom software as described previously. After marking the relevant periods of interest, the custom software can determine breath-by-breath ventilation and derive the values for each trait measurement. Specific details are available in references.

Statistical Analysis

Demographic and baseline characteristics were reported for the OSA + HIV-positive and OSA + HIV-negative participants, using median and interquartile range.

Each OSA trait was compared between PLWH + OSA and OSA control groups using linear mixed-effects modeling, which allowed us to include every observation for the trait of interest (i.e., rather than just use mean values for each subject) and consider each participant as a random-effect parameter. To decrease the variance and residual bias, all models were adjusted a priori for fixed effects of age, sex, and BMI. Parameter estimates are reported in the text as means ± standard error, and differences are reported as the mean difference with 95% confidence interval.

We calculated an 80% power to find a difference between groups of 0.5 standard deviations (i.e., small-to-moderate effect) using a sample size of 34 matched participants, at a two-tailed α of 0.05. A P value of <0.05 was considered statistically significant. The traits that were directly measured (V_{eupnea}, $V_{arousal}$, $V_{passive}$, V_{active}, and loop gain) were considered as primary outcomes; computed measures (arousal threshold and upper airway gain) were considered as secondary outcomes, given the inherent variability when combining multiple variables together. Given the small number of preplanned comparisons, multiple-comparison correction was not applied. Statistical analyses were performed in R (version 4.0.1; http://www.r-project.org), using RStudio (version 1.3.959) and packages lme4 (version 1.1–26) and ggplot2 (version 3.3.3).

Table 1. *Demographic, questionnaire, and baseline PAP adherence data*

	PLWH + OSA	OSA control	*P* value
n	17	17	
Age, yr	58 (54, 64)	58 (55, 66)	0.77
Male	17 (100%)	17 (100%)	>0.99
Body mass index, kg/m^2	31.1 (30.7, 31.6)	29.0 (27.5, 33.3)	0.59
Epworth Sleepiness Score	9 (5, 14)	5 (3, 8)	0.13
PSQI	7 (6, 8)	4 (3, 8)	0.26
SF-36 global	72 (55, 85)	84 (75, 92)	0.04
Uses CPAP every night (self-report)	11 (69%)	11 (69%)	>0.99
Smoking history			0.08
Never	5 (29%)	11 (65%)	
Past	10 (59%)	6 (35%)	
Current	2 (12%)	0 (0%)	
FEV1/FVC ratio	76 (70, 81)	80 (74, 82)	0.94

Data are shown as median (IQR) or *n* (%). *P* value from Welch's two-sample *t* test (continuous) or Fisher's exact test (categorical). CPAP, continuous positive airway pressure; FEV1, forced expiratory volume in 1 s; FVC, forced expiratory volume; HIV, human immunodeficiency virus; OSA, obstructive sleep apnea; PAP, positive airway pressure; PLWH, people living with HIV; PSQI, Pittsburg Sleep Quality Index; SF-36, 36-item short-form survey.

RESULTS

Participants

Twenty PLWH + OSA subjects were recruited, of whom data were not obtained for two participants, and one participant enrolled but did not complete the study procedures. Seventeen PLWH + OSA and 17 matched OSA controls were included in the analysis. Baseline demographic, questionnaire, and PAP adherence are reported in Table 1. In general, participants were middle aged and overweight to obese; all participants were male. PLWH + OSA individuals had nonsignificantly higher Epworth Sleepiness Scale (ESS) scores, despite using PAP.

Baseline PSG results are reported in Table 2. Polysomnographic OSA characteristics were similar between groups, although the rapid eye movement (REM) apnea-hypopnea index (AHI) appeared nonsignificantly higher and the sleep efficiency and sleep duration nonsignificantly lower in the PLWH + OSA group compared with the OSA controls.

OSA Traits

Group estimates and across group differences from the age- and BMI-adjusted mixed-effects model are summarized in Table 3. Unadjusted individual mean values and model-adjusted group estimates for the major measured traits are shown in Fig. 2.

V_{eupnea}.

A total of 334 measurements across 34 participants were obtained (159 in 17 PLWH + OSA and 175 in 17 OSA controls). In the adjusted model, there was no significant difference in eupneic ventilation between PLWH + OSA and OSA control groups (difference = 0.5 [95% confidence interval (CI) = −0.3 to 0.9] L/min, $P = 0.31$).

$V_{arousal}$.

A total of 310 measurements across 34 participants were obtained (140 in 17 PLWH + OSA and 170 in 17 OSA controls). In the adjusted model, there was no significant difference in ventilation just before arousal in PLWH + OSA and OSA control groups (difference = 0.3 [95% CI = −0.2 to 1.2] L/min, $P = 0.17$).

$V_{passive}$ and P_{crit}.

A total of 72 acceptable values were obtained in 31 participants (30 in 14 PLWH + OSA and 42 in 17 OSA controls). There was no significant difference in $V_{passive}$ between PLWH + OSA and OSA control groups (difference = 0.5 [95% CI = −2.3 to 3.4] L/min, $P = 0.73$). P_{crit} was also not significantly different between PLWH + OSA and OSA control groups (difference = −0.4 [95% = CI −3.2 to 2.5] cmH_2O, $P = 0.80$).

V_{active}.

A total of 212 V_{active} measurements were obtained in 32 participants (125 in 16 PLWH + OSA and 87 in 16 OSA controls). There was no significant difference in V_{active} between PLWH + OSA and OSA control groups (difference = −0.9 [95% CI = −3.4 to 1.7] L/min, $P = 0.51$).

Loop gain.

A total of 94 LG measurements across 27 participants were obtained (37 in 12 PLWH + OSA and 57 in 15 OSA controls). There was no significant difference in LG between PLWH + OSA and OSA control groups (difference = 1.1 [95% CI = −1.0 to 3.2], $P = 0.32$).

Arousal threshold.

A total of 279 arousal threshold measurements across 30 participants were calculated (113 in 14 PLWH + OSA and 166 in 16 OSA controls) from individual $V_{arousal}$ measurements and the subject's mean loop gain. There was no significant difference in arousal threshold between PLWH + OSA and OSA controls (difference = 2.5 [95% CI = −0.9 to 5.8] L/min, $P = 0.16$).

Upper airway gain.

A total of 197 upper airway gain values across 29 participants were calculated (111 in 14 PLWH + OSA and 86 in 15 OSA controls). There was no significant difference in UAG between PLWH + OSA and OSA control groups (difference = 0.4 [95% CI = −1.8 to 2.5], $P = 0.72$).

Table 2. *Baseline PSG results*

	PLWH + OSA	OSA control	*P* value
n	17	17	
Duration sleep, min	284 (248, 366)	316 (292, 343)	0.13
Sleep efficiency, %	69 (64, 87)	79 (73, 90)	0.09
NREM, %	89 (84, 97)	84 (81, 91)	0.11
REM, %	11 (3, 16)	16 (9, 19)	0.11
Arousal index, events/h	32 (23, 74)	31 (13, 42)	0.29
Total AHI, events/h	48 (28, 78)	44 (24, 58)	0.46
NREM AHI, events/h	47 (21, 78)	41 (19, 57)	0.49
REM AHI, events/h	48 (36, 73)	27 (20, 56)	0.37
Mean sleep SpO_2, %	93 (91, 94)	92 (91, 94)	0.38
Sleep with SpO_2 <90%, %	7 (3, 17)	2 (1, 17)	0.95
Nadir sleep SpO_2, %	83 (77, 85)	81 (78, 84)	0.42

Data are shown as median (IQR). *P* value from Welch's two-sample *t* test. AHI, apnea-hypopnea index; NREM, nonrapid eye movement; OSA, obstructive sleep apnea; PLWH, people living with HIV; PSG, polysomnography; REM, rapid eye movement.

Table 3. *Group estimates of OSA traits determined from physiological sleep study, adjusted for age and BMI*

	PLWH + OSA	OSA control	Difference [95% CI]	*P* value
V_{eupnea}, L/min	7.6 ± 0.2	7.1 ± 0.2	0.5 [−0.3 to 0.9]	0.31
$V_{arousal}$, L/min	6.1 ± 0.2	5.8 ± 0.2	0.3 [−0.2 to 1.2]	0.17
$V_{passive}$, L/min	1.2 ± 1.1	0.7 ± 1.0	0.5 [−2.3 to 3.4]	0.73
P_{crit}, cmH_2O	−2.3 ± 1.1	−1.9 ± 1.0	−0.4 [−3.2 to 2.5]	0.80
V_{active}, L/min	2.0 ± 0.9	2.8 ± 0.9	−0.9 [−3.4 to 1.7]	0.51
Loop gain	4.4 ± 0.8	3.3 ± 0.7	1.1 [−1.0 to 3.2]	0.32
Arousal threshold, L/min	14.5 ± 1.3	12.0 ± 1.1	2.5 [−0.9 to 5.8]	0.16
Upper airway gain	1.1 ± 0.8	0.7 ± 0.8	0.4 [−1.8 to 2.5]	0.72

BMI, body mass index; CI, confidence interval; HIV, human immunodeficiency virus; OSA, obstructive sleep apnea; PLWH, people living with HIV.

Sensitivity Analysis

When adding a covariate to the mixed-effects model with the sleep stage for each measurement, results were similar for estimated group differences in V_{eupnea} (0.5 [−0.2 to 1.2] L/min), $V_{arousal}$ (0.4 [−0.2 to 1.0] L/min), V_{active} (−0.8 [−3.4 to 1.7] L/min), loop gain (1.1 [−1.0 to 3.2] L/min), arousal threshold (2.2 [−1.2 to 5.6] L/min), and upper airway gain (0.3 [−1.8 to 2.5] L/min). Since V_{crit}/P_{crit} measurements span several sleep stages, it was not possible to adjust these traits for sleep stage.

DISCUSSION

In this study of traits responsible for OSA pathogenesis, we found no difference between PLWH with OSA and a comparable control group without HIV. Our method allows us to evaluate both the anatomical and nonanatomical contributors to OSA, neither of which appeared to be different in those with well-controlled HIV on modern therapies. Although our study included only persons with OSA, we anticipated that OSA traits would differ between the groups if HIV itself substantially affected OSA pathogenesis. Of note, our study included CPAP-treated individuals. It is felt that traits measured after CPAP treatment reflect "underlying" OSA pathogenesis, rather than physiological changes induced by OSA itself (21).

Because some studies suggest that OSA has a higher prevalence in PLWH, a number of theories have been proposed for how HIV might predispose to OSA. As noted previously, lipohypertrophy was associated with earlier ART regimens, particularly HIV protease-inhibitor treatments, and it has been proposed that fat accumulation may narrow the upper airway preferentially. This assertion may explain the finding that OSA occurs at lower BMIs in PLWH than in controls (11). Contemporaneous ART regimens are mostly HIV integrase inhibitor based, and newer integrase inhibitors have been associated with excessive weight gain as well. Consequences of this excessive weight gain and fat redistribution are being explored, and the link to OSA may yet be demonstrated. It is possible that a study focused on particular BMI subgroups who are most impacted by differential fat distribution may provide further physiological insights. OSA is a disease of aging (22), and increases in prevalence with age are partly due to the upper airway becoming more collapsible over time. Similarly, HIV is considered a disease of accentuated and accelerated aging, for example, changes in lung function are observed that are similar to senile emphysema (23). Nonetheless, we did not see systematic changes in upper airway collapsibility in PLWH/OSA participants relative to age- and BMI-matched controls with OSA but without HIV. HIV can also cause neuropathic or myopathic changes, and it has been proposed that such changes might limit upper airway

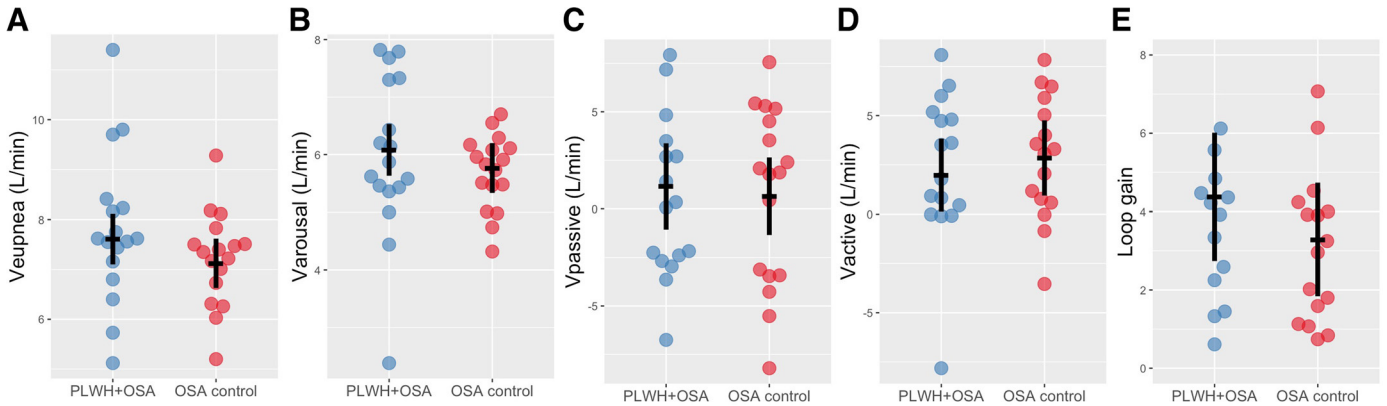

Figure 2. Measured OSA traits in HIV-positive individuals with OSA compared with matched HIV-negative controls with OSA. Dots are each individual's mean value from repeated measurements taken during sleep. The bar plot represents each group's estimated marginal mean and associated 95% confidence interval determined by mixed-effects modeling adjusted for age and BMI, as described in METHODS. *A*: V_{eupnea} (17 male PLWH + OSA, 17 male OSA controls) was not significantly different ($P = 0.31$). *B*: $V_{arousal}$ (17 male PLWH + OSA, 17 male OSA controls) was not significantly different ($P = 0.17$). *C*: $V_{passive}$ (14 male PLWH + OSA, 17 male OSA controls) was not significantly different ($P = 0.73$). *D*: V_{active} (16 male PLWH + OSA, 16 male OSA controls) was not significantly different ($P = 0.51$). *E*: loop gain (12 male PLWH + OSA, 15 male OSA controls) was not significantly different ($P = 0.32$). BMI, body mass index; HIV, human immunodeficiency virus; OSA, obstructive sleep apnea; PLWH, people living with HIV.

responsiveness leading to airway collapse. Changes in the respiratory threshold to arousal and control of breathing have been linked to OSA pathogenesis in HIV-comorbid medical conditions such as chronic heart and lung disease (24). Nonetheless, we did not observe a measurable impact of HIV on the pathogenesis of OSA in our study population.

Early diagnosis of OSA in PLWH may be important for several reasons. As discussed earlier, the reported prevalence of OSA in PLWH is quite high, at least in some cohorts. Ongoing studies should provide a more accurate assessment of the prevalence of OSA in PLWH with long-term suppression of the virus by modern ART regimens. Data on the prevalence of OSA in women living with HIV are also needed, particularly since the risk of excessive weight gain after ART initiation is higher in women than in men (25). The diagnosis of OSA is also likely to be important in understanding some of the more common clinical complaints reported by PLWH. For example, witnessed apnea, a specific marker of OSA, was the most important predictor for clinically relevant fatigue (26). Importantly, untreated moderate-to-severe OSA in PLWH is associated with increased inflammation measured by C-reactive protein and detectable HIV RNA (27). Interestingly, we noted that despite similar use of PAP among study participants, PLWH + OSA with HIV had higher levels of sleepiness as assessed by the ESS, worse sleep as assessed by PSQI, and decreased sleep time and sleep efficiency on the baseline PSG. Whether treatment of OSA improves fatigue in PLWH is the subject of ongoing research (NCT03575143).

Because our results suggest that the pathogenesis of OSA is similar in those with and without HIV, we propose that the approach to PLWH with OSA (suspected or confirmed) could be similar to that taken in persons without HIV. Because OSA is likely common and important for PLWH, we propose a low threshold for OSA screening and referral for sleep testing if screening is positive. Unfortunately, current data suggest that most PLWH with OSA are undiagnosed and untreated. For example, in a Veterans Administration Cohort, only 4% of PLWH were diagnosed with OSA (28). In contrast, more than 12% of those without HIV had been diagnosed with OSA. Similarly, in a University Center For AIDS Research Clinic (CFAR), only 4% of their patients were diagnosed with OSA (29). It may be that symptoms of fatigue and tiredness are often ascribed to HIV or ART rather than prompting investigation for another (treatable) cause (30).

Similarly, existing treatments for OSA should be adequate for treatment in PLWH. Although CPAP has high efficacy, adherence limits real-world effectiveness. Underlying OSA physiology is an important determinant of the response to other available OSA treatment such as oral appliances, upper airway surgery, hypoglossal nerve stimulation, and pharmacotherapy (31). Given similar underlying physiology and emerging clinical impacts of OSA in PLWH, non-CPAP treatments may also be considered as an alternative to CPAP in this group.

Limitations of our study should be noted. First, our study was of limited sample size, due to the complexity of such physiological studies. The confidence intervals surrounding the estimated differences between PLWH + OSA and OSA controls for each trait suggest against large differences, but smaller differences cannot be excluded. Emerging data provide some context of differences in OSA traits that might be clinically important. Oral appliance responders have been shown to have a $V_{passive}$ ~2.5 L/min higher than nonresponders (32). In our data, most of the 95% CI for the difference in $V_{passive}$ between HIV-positive and HIV-negative individuals was less than this value, suggesting that we are unlikely to miss important differences in $V_{passive}$. Smaller differences in traits have been observed to differ statistically among responders and nonresponders to hypoglossal nerve stimulation, but differences in arousal threshold and upper airway response on the order of ~30% are needed to increase substantially the odds of treatment success (33). Our data did not generally support such substantial differences being attributable to HIV itself, although within the entire cohort, there were differences across individuals that might allow prediction of non-CPAP therapies.

Second, different findings might be observed with different antiretroviral regimens. Current ART regimen data were collected, but the sample size limited inferences regarding the role of specific drugs in OSA causation. It may be that some older medications might cause lasting changes to the airway through fat or lymph tissue redistribution; however, we were not able to explore that hypothesis from our data, as our sample size was modest, and we did not systematically collect all prior medication exposures. Third, the population studied might differ from other groups of PLWH. We restricted enrollment to those who were adherent to both HIV medications and therapy for their OSA. Similarly, by selecting only those on PAP therapy, we may have selected a group of subjects who have a relatively normal respiratory arousal threshold, as low arousal threshold (wake up too easily) has been reported as a risk factor for PAP nonadherence (34). Moreover, patients adherent to PAP therapy are likely to be "healthy users" and may differ systematically from those who remain untreated (e.g., socioeconomic, motivation, and education influences) (35).

In conclusion, the anatomical and nonanatomical traits important for OSA are similar between those with and without HIV. Future work should determine the clinical impact of OSA treatment in PLWH.

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AUTHOR CONTRIBUTIONS

B.A.E., M.K., C.B.H., and R.L.O. conceived and designed research; J.E.O., C.N.S., P.N.D., and R.L.O. performed experiments; J.E.O., B.A.E., C.N.S., S.J., A.M., and R.L.O. analyzed data; J.E.O., B.A.E., C.N.S., M.K., C.D., R.T., A.M., C.B.H., and R.L.O. interpreted results of experiments; J.E.O. and B.A.E. prepared figures; J.E.O., M.K., A.M., and R.L.O. drafted manuscript; J.E.O., B.A.E., C.N.S., M.K., P.N.D., C.D., R.T., S.J., A.M., C.B.H., and R.L.O. edited and revised manuscript; J.E.O., B.A.E., C.N.S., M.K., P.N.D., C.D., R.T., S.J., A.M., C.B.H., and R.L.O. approved final version of manuscript.

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